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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/765,086	01/17/2001	Erkki I. Ruoslahti	P-LJ 4575	6131

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EXAMINER
YU, MISOOK

ART UNIT	PAPER NUMBER
1642	10

DATE MAILED: 05/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/765,086	Applicant(s) RUOSLAHTI ET AL.	
	Examiner Misook Yu	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *1-7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *8-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Seq. Alignment* .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of group II in Paper No. 9 is acknowledged. The traversal is on the ground(s) that the species election requirement is unnecessary for two reasons: (1) the elected group II only reads on the elected species; (2) the species are related and are a small number that there is no burden on the examiner for search them all. This examiner agrees with applicant that the species requirement is unnecessary on the ground for the reason (1) above, but not (2) above that group II reads on the elected species only, therefore the species election requirement for group II is withdrawn. Applicant does not argue about the two different election of one of the two inventions, groups I and II; this is treated as that applicant election of group II without traverse.

Claims 1-7 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9.

Claims 8-22 in its entirety as applicant suggested will be examined on merits.

Specification

The disclosure is objected to because of the following informalities: The instant application has seven panels (a-g) in Figure 2 but the specification of the figure legend at page 6 describes only two panels (a and b). The instant application has only two panels (a and b) in Figure 3 but the specification of the figure legend at page 7 describes four panels (a-d). To fully comply with 37 CFR 1.74, applicants are required that all figures are correctly described in the brief description of the drawing ***without introducing new matter***. See MPEP 608.01(f).

NOT fixed

The instant application at page 84 refers to nonexisting Figure 3c and 3d, and also at page 81 lines 7 refers to nonexistant Figure 2b, lane 4. Table 5 at page 104 is

fixed

the last table but the specification at 77 lines 25 and 26 alleges that Table 7 showing prostate homing peptides exists. Appropriate correction is required. Fixed

Claims 8 and 18 are objected to because it depends on a nonelected claim. Appropriate correction is required. fixed

For the purpose of this office action, however, the limitations of claim 1 will be included in the examination of the pending claims 8-22. However, this treatment does not relieve applicants the burden of responding to this objection.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8, 9, 13, 14, and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 8 and 13 refer to a nonelected claim 1, which recites "selectively internalized by prostate tissue" but it is not clear what the metes and bounds are for selectively internalized by prostate tissue.

Claims 8 and 13 refer to a nonelected claim 1, which recites "high toxicity" but it is not clear what the metes and bounds are for high toxicity.

Claims 8 and 13 refer to a nonelected claim 1, which recites "low mammalian cell toxicity" but it is not clear what the metes and bounds are for low mammalian cell toxicity. The instant specification at page 16 lines 8-12 states that low mammalian cell toxicity is not lytic to human erythrocytes. Is a microbial peptide "having low mammalian cell toxicity" if said antimicrobial peptide is lytic to human lymphocytes, lytic to dog erythrocytes, or mouse erythrocytes?

Claims 9, 14, and 19 recites "functionally equivalent sequence" but it is not clear what the metes and bounds are for "functionally equivalent sequence". Is the function

refers to the peptide properties of SEQ ID NO:207 or does the function refer to prostate-homing?

For the purpose of this office action, the examiner will assume that functionally equivalent sequence means prostate-homing peptide selected from phage display binds to human prostate vaculature (see Figure 9 and the corresponding figure legend at page 8, page 107 lines 9-25).

Claim 13 recites "selective toxicity" but it is not clear what the metes and bounds are for selective toxicity.

Claim 18 recites the limitation "said tumor" in line 4. There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8, 13, and 18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 8, 13, and 18 are drawn to method for directing cancer-killing peptide to prostate selectively, thereby treating prostate cancer ***by a genus of prostate-homing cancer-killing chimeras***. The specification provides evidence from page 106 lines 21 to page 107 line 6, Figures 7 and 8, and the corresponding figure legends at page 8 that only one chimera, the chimera used in Figure 7 and 8 is able to do the purpose stated in the preambles of instant claims 8, 13, and 18. . Based on only chimera that is able to perform the purpose stated in the preamble of the claims, one cannot predict the types of additional chimera which will show all the functions stated in the preamble stated in the claims. It is concluded that applicants adequately describes only one chimera in shown claim 12 and used in Figure 7 and 8.

Claims 9, 14, and 19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 9, 14, and 19 are drawn ***a genus of prostate-homing peptides***. The specification provides evidence at page 107 lines 9-25, Figure 9 and the corresponding figure legend at page 8 that only one such peptide, SEQ ID NO:207 is able to selectively bind to prostate tissue . Based on only one peptide with selective prostate-homing ability, one cannot predict the types of additional peptides which will show all the functions exhibited by SEQ ID NO:207 at page 107 lines 9-25, Figure 9. Since the genus includes a large number of unpredictable species, possession of only one species is not seen as sufficient to reasonably convey possession of the entire genus. It is concluded that applicants adequately describes SEQ ID NO:207 that is able to target antimicrobial peptide to prostate tissue.

Claim Rejections - 35 USC § 103

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim 8, 13, and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arap et al (16 January 1998, Science Vol. 279, 377-380), Fossa et al (1997, European urology 31 Suppl 3 p3-8, abstract only), and US Pat. 5,789,542 (IDS, 4 August, 1998), and WO 90/12866 (01 November, 1990), Javadpour et al (IDS, 1996, J. med. Chem. Vol. 39, 3107-3113), Bessalle et al (IDS, 1990, FEBS Lett. 274, 151-155) and Alvarez-Bravo et al (IDS, 1994, Biochem. J. 302, 535-538).

Claim 8, 13, and 18 are drawn to method for treating patients with prostate cancer with a chimera comprising prostate-targeting peptide and antimicrobial peptide.

Arap et al (16 January 1998, Science Vol. 279, 377-380) teach that it is possible using phage display assay to identify peptides that that could deliver drugs specifically to the vasculature of specific tumor blood vessels because endothelial cells in the angiogenic vessels within solid tumors express several proteins that are absent or barely detectable in established blood vessels (see the first paragraph of column 1, page 377). Arap et al further teach that successful treatment of mice bearing human breast carcinoma with several peptides that stick to molecules found only in the tumor-associated blood vessels (Fig. 3 and 4) and suggest that vivo selection of phage peptide libraries to identify peptides that home to a specific tumor vasculature have the potential to markedly improve cancer treatment and this approach could be applicable to many other human cancers (column 6, the last paragraph, page 380). Arap et al does not mention prostate cancer or an antimicrobial peptide that could kill cancer cells.

However, Fossa et al teach that overall life quality of patient's undergoing various currently available treatments for prostate cancer suffers significantly because the currently available treatments cause generalized toxic effects throughout the patient's body and addresses need for treatment that could mimize generalized toxic effects. WO 90/12866 teaches antimicrobial peptides that could induce lysis of cancer cells (see abstract) and teaches a specific peptide that comprises SEQ ID NO:200 of the instant application (see the sequence alignment along with the summary included in the sequence alignment and see claim 24). Further US Pat. 5,789,542 teaches the antimicrobial peptide for treating cancer is identical to SEQ ID:200 of the instant application (see the sequence alignment) and teaches how to make the peptide and how to assay the synthesized peptides for their activity in column 6, line 45 through column 12 last line. Javadpour et al further teaches that SEQ IDNO:200 of the instant application has antimicrobial property while maintaining low mammalian cytotoxicty (see the abstract, column 3 2nd paragraph and Table 1). Bessalle et al teach in the abstract, column 1 last paragraph to first paragraph of column 2 at page 151 that all-D-enamtiomer of peptide might possess biological property similar to those of the

respective natural L-enantiomer and the all-D-enamtiomer are highly resistant to proteolysis. Further, Alvarez-Bravo teaches at the abstract that all-D-enamtiomer peptide show greater antimicrobial activity than the corresponding L-enantiomer. Degradation-resistant therapeutic peptide is easier to handle than degradation-prone peptide, which in turn leads to more cost effective manufacturing of anti-cancer drug. Degradation-resistant therapeutic peptide will increase in vivo half life of the chimeric prostate-homing pro-apoptotic peptide, thereby less frequent injection to the prostate cancer suffering patients.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to combine teachings of all of the above references to make a chimera with ability to kill prostate cancer cells selectively without causing generalized toxic effect to improve overall quality of life of prostate cancer patients.

Claims 9, 14, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arap et al (16 January 1998, Science Vol. 279, 377-380), Fossa et al (1997, European urology 31 Suppl 3 p3-8, abstract only), and US Pat. 5,789,542 (IDS, 4 August, 1998), and WO 90/12866 (01 November, 1990), Javadpour et al (IDS, 1996, J. med. Chem. Vol. 39, 3107-3113), Bessalle et al (IDS, 1990, FEBS Lett. 274, 151-155) and Alvarez-Bravo et al (IDS, 1994, Biochem. J. 302, 535-538) as applied to claims 8, 13, and 18 above, and further in view of WO 99/46284 (IDS).

Claims 9, 14, and 19 are drawn to method of for treating patients with prostate cancer with a chimera comprising a specific prostate-targeting peptide identified as SEQ ID NO:207. SEQ ID NO:207 of the instant application is identical to the peptide sequence SEQ ID NO :21 of (see the sequence attachment) and Table 1 of WO 99/46284 teaches that the sequence is prostate-homing sequence.

Claims 10, 15, 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arap et al (16 January 1998, Science Vol. 279, 377-380), Fossa et al (1997,

European urology 31 Suppl 3 p3-8, abstract only), and US Pat. 5,789,542 (IDS, 4 August, 1998), and WO 90/12866 (01 November, 1990), Javadpour et al (IDS, 1996, J. med. Chem. Vol. 39, 3107-3113), Bessalle et al (IDS, 1990, FEBS Lett. 274, 151-155) and Alvarez-Bravo et al (IDS, 1994, Biochem. J. 302, 535-538) as applied to claims 8, 13, and 18 above, and further in view of Ellerby et al (IDS, September 1999, Nature Medicine 5, 1032-1038), Bessalle et al (IDS, 1990, FEBS Lett. 274, 151-155) and Alvarez-Bravo et al (IDS, 1994, Biochem. J. 302, 535-538), Javadpour et al (IDS, 1996, J. med. Chem. Vol. 39, 3107-3113).

Claims 10, 15 and 20 are drawn to method for treating patients with prostate cancer with a chimera comprising the specific antimicrobial peptide of all-D enantiomer of SEQ ID NO:200 of the instant application.

Ellerby et al teaches in the Fig.1, a peptide comprising the specific peptide shown in the claims.

Bessalle et al teach in the abstract, column 1 last paragraph to first paragraph of column 2 at page 151 that all-D-enamtiomer of peptide might possess biological property similar to those of the respective natural L-enantiomer and the all-D-enamtiomer are highly resistant to proteolysis. Further, Alvarez-Bravo teaches at the abstract that all-D-enamtiomer peptide show greater antimicrobial activity than the corresponding L-enantiomer. Degradation-resistant therapeutic peptide is easier to handle than degradation-prone peptide, which in turn leads to more cost effective manufacturing of anti-cancer drug. Degradation-resistant therapeutic peptide will increase in vivo half life of the chimeric prostate-homing pro-apoptotic peptide, thereby less frequent injection to the prostate cancer suffering patients.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to combine the three teachings to make all-D-enamtiomer to avoid degradation by proteases.

Claims 11, 12, 16, 17, 21, 21, and 22 are rejected under 35 U.S.C. 103(a) as being obvious over WO 99/46284 above as applied to claims 9, 14, 19 and Ellerby et al above as applied to claims 10, 15, and 20, further in view of Arap et al (16 January

1998, Science Vol. 279, 377-380), Fossa et al (1997, European urology 31 Suppl 3 p3-8, abstract only), and US Pat. 5,789,542 (IDS, 4 August, 1998), and WO 90/12866 (01 November, 1990), Javadpour et al (IDS, 1996, J. med. Chem. Vol. 39, 3107-3113) as applied to Claim 8, 10, 13, 15, 18, and 20.

Claims 11, 12, 16, 17, 21, 21, and 22 are drawn to treating prostate with cancer with a specific prostate-homing cancer-killing chimera shown in the claims.

WO 99/46284 teaches the prostate-homing part of the specific chimera and Ellerby et al teaches the cancer-killing part of the microbial peptide, and the coupling domain of GG in Fig. 1 and the rest of the references teaches why it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to motivated to make the chimera shown in the claims to treat prostate cancer.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Misook Yu whose telephone number is 703-308-2454. The examiner can normally be reached on 8 A.M. to 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Misook Yu, Ph.D.
May 20, 2002

MARY E. MOSHER
PRIMARY EXAMINER
GROUP 1800
1600